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Review Article

Establishing gold standard approaches to rapid tranquillisation: A review and discussion of the evidence on the safety and efficacy of medications currently used

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Abstract

Background: Rapid tranquillisation is used when control of agitation, aggression or excitement is required. Throughout the UK there is no consensus over the choice of drugs to be used as first line treatment. The NICE guideline on the management of violent behaviour involving psychiatric inpatients conducted a systematic examination of the literature relating to the effectiveness and safety of rapid tranquillisation (NICE, 2005). This paper presents the key findings from that review and key guideline recommendations generated, and discusses the implications for practice of more recent research and information.
Aims: To examine the evidence on the efficacy and safety of medications used for rapid tranquillisation in inpatient psychiatric settings.
Method: Systematic review of current guidelines and phase III randomised, controlled trials of medication used for rapid tranquillisation. Formal consensus methods were used to generate clinically relevant recommendations to support safe and effective prescribing of rapid tranquillisation in the development of a NICE guideline.
Findings: There is a lack of high quality clinical trial evidence in the UK and therefore a `gold standard' medication regime for rapid tranquillisation has not been established.
Rapid tranquillisation and clinical practice: The NICE guideline produced 35 recommendations on rapid tranquillisation practice for the UK, with the primary aim of calming the service user to enable the use of psychosocial techniques.
Conclusions and implications for clinical practice: Further UK specific research is urgently needed that provides the clinician with a hierarchy of options for the clinical practice of rapid tranquillisation.

Keywords

Rapid tranquillisation; violence; aggression; antipsychotic; benzodiazepine

INTRODUCTION

Rapid tranquillisation or urgent sedation (Broadstock, 2001), is used in situations requiring the rapid control of agitation, aggression or

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excitement in adult psychiatric inpatients where de-escalation techniques have not proved sufficient in themselves. Although the use of high dose antipsychotics for this purpose has been criticised by several inquiries (Royal College of Psychiatrists, 1997), expert clinician opinion, has in exceptional circumstances, supported prescribing outside the dose limits stated in the British National Formulary (BNF) in order to achieve rapid tranquillisation.

Very few randomised controlled trials have been conducted which examine the safety and efficacy of medicines that are used for rapid tranquilisation. In recent years there has been a general reduction in the range of doses that are used. This shift in practice coincides with the changes in the stated aim of rapid tranquillisation over recent years: to induce a state of calm, rather than sleep (Cunnane, 1994; Beer et al., 2001; Burgess, 1997).

A systematic review on rapid tranquillisation was conducted for the National Institute of Health and Clinical Excellence (NICE) guideline on the short-term management of disturbed/violent behaviour in psychiatric inpatient settings and emergency departments. This paper presents the key results of that review, notes more recent research and changes in medication Summary of Product Characteristics (SPC). The implications for practice are discussed in the light of the key recommendations for rapid tranquillisation from the guideline.

BACKGROUND

Benzodiazepines and antipsychotics either alone or in combination are commonly used in the UK for rapid tranquillisation. The oral route is preferred, but when refused drugs are administered parenterally. When diazepam is administered intramuscularly its absorption is slow and erratic and with repeated doses is associated with prolonged sedation. Lorazepam, has a shorter elimination half-life than many other benzodiazepines, which may limit the risks associated with dose accumulation. All the benzodiazepines carry a risk of respiratory depression when used in high doses or in combination with other hypnosedatives (Broadstock, 2001).

Although antipsychotics are considered to be a second line treatment they can be used as first line where benzodiazepines are contra-indicated or have been ineffective. Conventional antipsychotics have a greater propensity to cause extrapyramidal side effects (EPS) than the atypical antipsychotics.

In some areas it is common practice to co-administer both a benzodiazepine and antipsychotic together. This is thought preferable by some clinicians who consider the practice enables behavioural control to be achieved without the need for resorting to higher doses of antipsychotics (Holmes et al., 2001).

The two main areas of concern when using antipsychotics for rapid tranquillisation are the induction of extrapyramidal side effects and adverse cardiac events (see Box 1). Extrapyramidal side effects are mostly associated with conventional antipsychotics. Side effects such as dystonia and akathisia are distressing and unpleasant for the service user. Experiencing these at the time of initial contact with psychiatric services may adversely affect a patient's preparedness to access either treatments or services. The availability of atypical antipsychotic drugs provides some hope that these adverse effects can be avoided.

This paper presents the relevant findings of the evidence review used to generate the NICE guideline recommendations for the practice of rapid tranquillisation for the short term management of violence in psychiatric inpatients and emergency departments. Key studies published since the review was conducted, changes in the SPC for haloperidol and the implications for the current recommendations with reference to the UK context are discussed.

REVIEW METHODS

Aim of the review

To examine the evidence on the efficacy and safety of medications currently used for rapid

Box 1. Risk of adverse cardiac events

Although rare, life threatening cardiac disturbances may be induced by antipsychotic drugs when used for rapid tranquilisation. In some cases these drugs may affect cardiac ventricular repolarisation (the QT interval). A number of factors such as physical exertion and stress may also impact on the QT interval.

QTc interval is a useful, if somewhat imprecise indicator of the risk of cardiac events. Prolongation can be congenital or acquired. Service users who already have prolonged QTc are at risk of developing an arrhythmia when given drugs which further lengthen the QT interval. Service users with torsades de pointes, left ventricular dysfunction or hypertrophy and liver disease are at an increased risk (Day et al., 1993). Additional risk factors also include diuretics or other arrhythmogenic drugs. Females tend to have a longer QT interval on average than men, which therefore increases their risk of torsades de pointes (Rautaharju et al., 1992; Makkar et al., 1993).

The relationship between antipsychotics, ventricular tachycardia and sudden cardiac death is not straight forward. QT prolongation and resulting arrhythmias are generally dose related (Drici et al., 1998; Warner et al., 1996; Reilly, 2000; Ray et al., 2001). It is also important to note that several case reports of sudden death involved agitated service users who were subject only to physical interventions. Other factors implicated in the increased risk of arrhythmia include the use of the illicit drugs such as ecstasy (Drake & Broadhurst, 1996) and cocaine (Pereira et al., 1997).

tranquillisation within psychiatric inpatient settings in the UK.

Inclusion criteria

Systematic reviews through to Phase III randomised controlled trials. All adults 16 years and over in inpatient psychiatric settings applicable to the UK.

Exclusion criteria

Those with organic brain disorders or progressive neurological dysfunction, learning disability or dual diagnosis.

Types of outcome

Efficacy and safety of the various medications used for rapid tranquillisation

Searching, critical appraisal and data extraction

The methods adopted in this review are those outlined in Eccles & Mason (1998) and in the NICE Technical Manual (2004). An extensive search of the literature was undertaken. Searches were run from 1969–2003. All major databases including Medline, CINAHL, PSYCHINFO, grey literature databases SIGLE and HMIC were searched. For a complete list of databases searched and search terms used, including those used by the Royal College of Psychiatrists see Royal College of Nursing (2005). Searches were not limited by study design, or to English language citations. Hand searching was not undertaken following NICE advice that exhaustive searching on every guideline review topic is not practical or efficient (Mason et al., 2002).

Titles and abstracts were retrieved and reviewed by two researchers for eligibility. Relevant papers were ordered. Study appraisal and methodological quality were assessed using checklists designed with assistance from the Centre for Statistics in Medicine at Oxford University.

Data was abstracted by a single reviewer and evidence tables compiled. All included articles were subject to quality assessment by a second reviewer. Any discrepancies between reviewers were resolved by discussion. Where needed, a third reviewer assisted with decisions on the inclusion or exclusion of a study. Full details of data abstraction, sifting, and reviewing processes can be found in Royal College of Nursing (2005).

DATA SYNTHESIS

Quantitative analysis was considered inappropriate for this review, as advised by methodological experts. Summary statistics of significance are reported in the evidence tables in Royal College of Nursing (2005). All possible medications were considered in the review however, only those currently licensed for use in the UK will be reported here.

EVIDENCE SUMMARY

From 153 studies identified in the initial sift, 20 papers detailing phase III randomised controlled trials were retrieved. One was excluded because

it was already included in a specific medications systematic review which forms part of the evidence base of this review. One of these studies reported on two different trials (Garza-Trevino et al., 1989). Unless otherwise stated, all studies considered the intramuscular (i/m) route. Some studies switched to oral formulations after the first 24hrs; where this occurs it is indicated in the evidence tables (Royal College of Nursing, 2005).

Seven of nine systematic reviews identified proved relevant to the research question. Three of these had similar aims to the NICE evidence review (Royal College of Psychiatrists, 1998; National Collaborating Centre for Mental Health, 2002; Broadstock, 2001). Studies included in these reviews were independently assessed and those not excluded form part of the evidence base for the review. Only systematic reviews to phase III randomised controlled trials are included.

The other four systematic reviews looked at specific medications for rapid tranquillisation. Dual diagnosis was not considered in the review.

Appraisal of methodological quality

Common methodological shortcomings were:

- Inappropriately small sample sizes (number needed to treat (NNT) not always stated or sufficient)
- Participants not always sufficiently agitated to require rapid tranquillisation
- Outcome measures not always sufficiently defined
- Intention to treat analysis not always clearly described
- Statistical measures, odds ratio (OR), relative risk (RR) and confidence intervals (CI) not clearly reported
- Different comparator medications, doses and outcomes were reported (e.g. sleep as both a desired endpoint and as an adverse effect)
- Poorly defined terminology which further complicated any comparison
- Follow-up periods different across studies
- Most studies did not report their method of randomisation nor how they ensured blinding/lack of bias.

FINDINGS

Clotiapine, ziprasidone, loxapine and thiothixene will not be discussed as they are not licensed in the UK. Neither will droperidol as it was voluntarily withdrawn by the manufacturer, Janssen-Cilag Ltd, from the end of March 2001, amid concerns over the medication's safety as an oral treatment for chronic conditions. Cost effectiveness of production resulted in other forms of the medication also being withdrawn. It is now unavailable in the UK for rapid tranquillisation.

Conventional antipsychotics

Chlorpromazine

Reschke (1974) compared i/m chlorpromazine 25mg, i/m haloperidol 5mg, 2mg, 1mg, and i/m placebo. Aggression was significantly more effectively controlled with i/m haloperidol 5mg and 2mg compared to i/m haloperidol 1mg, i/m chlorpromazine 25mg or i/m placebo. More adverse reactions were noted with haloperidol (transient hypertension, drowsiness, dry mouth and mild EPS) than chlorpromazine, although there was greater somnolence with chlorpromazine. The study had a very small sample size. Most participants in this study were women. Chlorpromazine i/m is no longer considered a suitable medication for rapid tranquillisation (Royal College of Psychiatrists, 1997).

Haloperidol

Haloperidol is recommended as the medication of choice in a number of national guidelines (McAllistair-Williams & Ferrier, 2004). A number of randomised controlled trials (reported below) consider the effectiveness and safety of haloperidol in relation to other medications:

- Olanzapine – Brier et al., 2002; Wright et al., 2001
- Ziprasidone – Brook et al., 2000
- Loxapine – Tuason, 1986; Fruensgaard et al., 1977; Paprocki & Versiani, 1977
- Lorazepam – Foster et al., 1997; Battaglia et al., 1997, Bieniek et al., 1998; Garza-Trevino et al., 1989
- Midazolam – Wyant et al., 1990.

Two further trials (Binder & McNiel, 1999; Dorevitch et al., 1999) evaluated the efficacy and safety of i/m haloperidol against i/m flunitrazepam and i/m molindone. Neither of these studies showed a significant difference between haloperidol and the other medication in terms of effectiveness. Flunitrazepam showed a slightly quicker reduction in aggression at 30 minutes but this did not reach significance at 90 minutes on the Overt Agitation Scale (Yudofsky et al., 1997). Molindone showed slightly less reduction in symptoms at 3 hours. Erythema at injection site was slightly more common for molindone than haloperidol. This side-effect is not discussed in relation to i/m flunitrazepam. Both studies had small sample sizes and neither used objective measures to evaluate behaviour at baseline. In the study of molindone there was no adjustment to the p value to account for the many comparisons and outcomes (outcomes were not restricted to rapid tranquillisation). It was also difficult to assess whether side effects resulted from the oral phase of the intervention. No firm conclusion can be reached about the relative superiority of these medications compared to haloperidol, although both flunitrazepam and molindone appear to be reasonably safe and effective within these trials.

Garza-Trevino et al., (1989) considered i/m thiothixene in combination with i/m lorazepam against i/m haloperidol in combination with i/m phenobarbital (see below for details). All studies suggest that haloperidol appears to be a reasonably safe and effective medication for rapid tranquillisation. Thiothixene is not licensed for use in the UK.

The SPC for haloperidol (Haldol) has been updated to include a requirement for baseline ECG prior to treatment. ECG is recommended prior to treatment in all patients, especially in the elderly and patients with a positive personal or family history of cardiac disease or abnormal findings on cardiac clinical examination. During therapy, the need for ECG monitoring (e.g. at dose escalation) should be assessed on an individual basis. Whilst on therapy, the dose should be reduced if QT is prolonged, and haloperidol should be discontinued if the QTc exceeds 500 ms. Inevitably, this has clinical implications for using haloperidol for rapid tranquillisation in situations where it has not been possible to obtain an ECG prior to initiating treatment. In such circumstances the use of haloperidol would be considered 'off label'. Prescribing medicines in this way alters (and probably increases) the prescriber's professional responsibility and potential liability.

Zuclopenthixol acetate

A high quality systematic review (Gibson et al., 2001) looked at the efficacy of zuclopenthixol acetate for use in emergency psychiatry. The review concluded that this medication was currently only justified in terms of clinical (i.e. expert opinion), rather than research, evidence. No further studies of zuclopenthixol acetate were identified by our searches. Reviewers noted that zuclopenthixol acetate is slow acting and therefore is normally no longer recommended for rapid tranquillisation. Furthermore, it has been noted that a number of sudden deaths and fatal cardiac events have been reported to the Medicines Control Agency (MCA) in the UK in relation to zuclopenthixol acetate (McAllistair-Williams & Ferrier, 2004).

Atypical antipsychotics

Risperidone

One systematic review (Aleman & Kahn, 2001) looked at the efficacy risperidone. There were some quality concerns with this review. The review considered this medication's function for the management of aggression, but excluded a study because it looked specifically at violence. There were additional quality issues underlying this exclusion. Some attempt was made to counter the heterogeneity of the studies by carrying out analyses of only double-blinded randomised studies and those with similar doses in order to assess the significance of various methodological differences between the studies. The reviewers note that risperidone is not available as an intramuscular preparation for acute use, which further limits its suitability for an emergency situation. The authors' conclusions on the efficacy and appropriateness of risperidone appear to be overly optimistic in relation to

the evidence base and should, therefore, be interpreted with caution.

Olanzapine

Two trials (Brier et al., 2002; Wright et al., 2001 – sponsored by Eli Lilly) evaluated i/m olanzapine against i/m haloperidol and against i/m placebo. Both studies were large multi-site, multi-country studies (571 participants in total). It is unclear whether the participants actually required rapid tranquillisation since all gave consent before being included in the study. Objective measures of behaviour were used in both studies at baseline (Positive and Negative Syndrome Scale (PANSS); Kay et al., 1992). There was no long term follow up with either study. Wright et al. (2001) found that both olanzapine and haloperidol were significantly more effective than placebo in reducing agitation at 2 and 24 hours in both studies. At 30 minutes, a dose of 5.0mg, 7.5mg or 10mg was significantly more effective that placebo. Olanzapine was significantly more effective than haloperidol in reducing agitation at 15, 30 and 45 minutes. The group sizes in Brier et al. (2002) did not allow comparison with placebo. Acute dystonia was not associated with olanzapine, but was found in 7% of the haloperidol group (Wright et al., 2001). Brier et al. (2002) also found that olanzapine was not associated with dystonia. There were no differences between olanzapine, haloperidol and placebo in terms of hypotension and clinically relevant changes in the QTc interval (Brier et al., 2002). On this basis Brier et al. (2002) suggested that olanzapine has a safer profile than haloperidol. For a meta-analysis of these two studies which slightly favours olanzapine see the NICE schizophrenia guideline (National Collaborating Centre for Mental Health, 2002). The manufacturers of olanzapine advise prescribers against the use of olanzapine outside the SPC recommended dose as severe adverse effects have been recorded.

Subsequent to the review, a further trial (Raveendran et al., 2007) evaluated i/m olanzapine against haloperidol in combination with promethazine. This trial was conducted in Vellore, India and is part of the TREC-India II collaborative group. 300 participants were randomised and followed up at 15, 30, 60, 120, 240 minutes after administration of medication. Inter-rata reliability in assessing severity of violent incidents and rating of outcome measures of tranquil/asleep was conducted. Patients were eligible if a relative was available to give consent. This study focussed on the effectiveness of the medications to remain effective over time. Olanzapine was more likely to calm (as oppose to sleep) patients within 1 hour, however, the effects wore off after that time and resulted in 17% more than the haloperidol with promethazine group receiving additional medical assessment. Haloperidol with promethazine was found to rapidly calm patients with most asleep and this was maintained over 4 hours. The authors conclude that in a situation where medical resources are scarce haloperidol with promethazine would be the better option. However, a sedated patient's vital signs should be monitored more closely and this is likely to impact on nursing and medical resources.

Benzodiazepines

Lorazepam

Two studies compared the benzodiazepine i/m lorazepam with the conventional anti-psychotic i/m haloperidol (Foster et al., 1997; Battaglia et al., 1997). Foster et al. (1997) noted no significant difference between the agitation scores for lorazepam and haloperidol at 1 hour on the Brief Psychiatric Rating Scale (BPRS; Overall & Gorham, 1962) but did note a significant difference in favour of lorazepam at 1 hour on the Clinical Global Impression scale (CGI; Guy, 1976). Battaglia et al. (1997) noted no significant difference between haloperidol and lorazepam at 1 hour, based on mean Agitated Behaviour Scale (ABS; Corrigan, 1989). Battaglia et al. (1997) and a further study (Garza-Trevino et al., 1989) considered the efficacy and safety of these two medications against a combination of haloperidol and lorazepam. Battaglia et al. (1997) noted a significant difference between haloperidol and combination at 1 hour, based on ABS score and between lorazepam and the combination at 1 hour based on ABS score. However, it is unclear if the combination would have been superior if the dose of the single agents had been equivalent to that of the combination.

Garza-Trevino et al., (1989) found the combination was more likely to lead to tranquillisation in 30 minutes. Bieniek et al., (1998) only considered the efficacy and safety of haloperidol against that of a combination of haloperidol and lorazepam. Non-parametric tests indicated that a greater percentage of participants improved post 60 minutes in the combined group. The studies had a number of limitations that meant that meta-analysis was not considered appropriate. Garza-Trevino et al. (1989) was not double-blinded, Battaglia et al. (1997) considered sleep as a desirable endpoint (the other studies did not) and combination doses were not equivalent to single medication doses. In terms of efficacy, no study found the antipsychotic to differ from the benzodiazepine. However, given the side effects caused by haloperidol (e.g. dystonia), all authors suggested that lorazepam might be the preferred course of treatment.

Midazolam

The study of i/m haloperidol vs i/m midazolam or i/m sodium amytal (Wyant et al., 1990) randomly assigned participants to either i/m haloperidol 10mg, i/m midazolam 5mg or i/m sodium amytal 250mg. Over 2 hours i/m sodium amytal and i/m midazolam proved significantly more effective than haloperidol in terms of mean global ratings for motor agitation, but there was no significant difference in hostility rating. This study has several limitations: very small sample size, only single blinded, insufficient data in the paper, and side effects are not mentioned. The authors recognise the need for a large scale future study comparing midazolam with lorazepam. The study of midazolam used sleep as a desirable endpoint, making comparisons with other studies difficult.

Another study considered midazolam and lorazepam against haloperidol plus promethazine (please see below).

Combination studies

Thiothixene & lorazepam vs haloperidol & phenobarbital

One study considered the use of i/m thiothixene in combination with i/m lorazepam against i/m haloperidol in combination with i/m phenobarbital (Garza-Trevino et al., 1989). This study was not double-blinded, there was a very short follow up period (24hr) and side effects were not described, although the authors claim that there were few indications of over-sedation or dystonic reactions. There appeared to be no difference in effectiveness between the two groups. The authors argue therefore that a combination of antipsychotic and a hypnosedative is a useful intervention for the management of agitated behaviour. It is difficult to generalise concerning the effectiveness and safety of these medication combinations on the basis of only one study given the various limitations noted above.

Haloperidol plus promethazine (vs lorazepam, vs midazolam)

One study (TREC Collaborative Group, 2003) compared i/m haloperidol-promethazine with i/m midazolam. Clinicians decided doses within a range of 7.5–15mg of i/m midazolam and 5mg of i/m haloperidol plus 25–50mg i/m promethazine. More somnolence was noted in the midazolam group. One man suffered respiratory depression with i/m midazolam 15mg and recovered after being given (i/v) flumazenil 0.25mg. One woman with epilepsy suffered a grand mal seizure with i/m haloperidol 5mg and i/m promethazine 50mg. When ratios of those either asleep or tranquil at 1 hour are considered, the study favours midazolam. However, a larger percentage of these patients were asleep in the midazolam group than in the haloperidol and promethazine group (93% compared to 87%). If only those patients who were tranquil at 1 hour are considered, the treatment favours haloperidol plus promethazine. No definitions are provided for tranquil or asleep.

Alexander et al. (2004) compared i/m haloperidol and i/m promethazine combined with i/m lorazepam. Doses were haloperidol 10 mg plus promethazine 25–50mg or lorazepam 4mg. Haloperidol i/m plus promethazine i/m was significantly more likely to induce sleep for all time periods. Haloperidol i/m plus promethazine i/m also resulted in quicker onset of tranquillisation/sleep. Four people in lorazepam group were never tranquil, One person in the haloperidol plus promethazine group was never

tranquil. No adverse reactions were noted with haloperidol plus promethazine. One person in the lorazepam group with history of bronchial asthma complained of moderate worsening of respiratory difficulty. Another person reported nausea and dizziness. There was no dystonia. Sleep was considered the desirable endpoint. When ratios of those either asleep or tranquil at 1 hour are considered, the study favours haloperidol plus promethazine. However, a larger percentage of these patients were asleep in the haloperidol and promethazine group than in the lorazepam group. If only those patients who were tranquil at 1 hour are considered, the treatment favours lorazepam.

Alexander et al. (2004) considered sleep the primary desirable outcome. The study did, however, detail numbers asleep and numbers tranquil at each endpoint. Alexander et al. (2004) argued that sleep is a safer option for staff, however, no significant difference in injury rates were noted with lorazepam, which was less sleep inducing. Neither study mentioned whether monitoring procedures, e.g. observation, ECG, etc. were put in place once participants were classified as asleep. There is disagreement between the studies as to whether haloperidol plus promethazine is actually more likely to induce sleep than a benzodiazepine. The studies suggest that haloperidol plus promethazine may be effective in rapid tranquillisation when sleep is a desirable outcome. However, if tranquil (calm) is the desirable endpoint, lorazepam alone is favoured. Few patients treated with i/m haloperidol plus i/m promethazine suffered dystonic reactions.

Both studies were large studies of a high methodological quality. However, after consultation with two independent methodological advisers, it was decided that meta-analysis would not be appropriate for the following reasons:

- It is unclear that midazolam and lorazepam are sufficiently similar clinically to be treated as a single class.
- The dose used may not be equivalent.
- Different time points were used (TREC Collaborative Group (2003) – 4 hours; Alexander et al. (2004) – 15mins) masking differences in effect when combined.
- TREC Collaborative Group (2003) took measurements at 20mins, but not with blinded raters.

These studies have also been reviewed in a Cochrane review (Huf et al., 2004), which concluded midazolam has a faster onset than lorazepam, however both benzodiazepines have potential to cause respiratory depression. Therefore Huf et al. (2004) favoured haloperidol with promethazine as the combination of choice for rapid tranquillisation. Outcome measure was tranquil or asleep. The studies were conducted in Rio, Brazil and Vellore, India. Subsequent to the NICE review (NICE, 2005) another trial conducted by the same group in Rio compared haloperidol with promethazine with haloperidol alone. This study found no evidence of benefit and significant evidence of harm in administering haloperidol alone (Huf et al., 2007).

The NICE guideline evidence review concluded that:

- There appear to be no conclusive benefits in terms of effectiveness of one antipsychotic over another, of antipsychotics over benzodiazepines or of combination medications over single medication regimes for rapid tranquillisation.
- The body of evidence suggests rapid tranquillisation as an intervention for the short-term management of disturbed/violent behaviour is both reasonably effective and reasonably safe. This evidence suggests that both benzodiazepines and antipsychotics appear to be effective and reasonably safe for use in rapid tranquillisation.
- It is not possible to determine the safety or effectiveness of medications other than antipsychotics and benzodiazepines for rapid tranquillisation.

For a detailed account of the NICE guideline review studies considered please see the evidence tables in the full version of the Violence guideline, appendix 2 (NICE, 2005).

Rapid tranquillisation and clinical practice

The GDG used formal consensus techniques to generate clinically relevant recommendations.

This was based on the available evidence at the time of the review and on clinical expertise. The guideline has 35 recommendations for the practice of rapid tranquillisation in the context of the short term management of disturbed/violent inpatients. The recommendations cover the use of both oral and parenteral medications, safety and aftercare of the service user. For a full list of the recommendations for clinical practice see full and short form versions of the violence guideline (NICE, 2005).

Only key recommendations pertinent to the focus of this paper are reported and are listed in Table 1 alongside indications, contra indications and restrictions for use.

DISCUSSION

The work of the TREC groups have substantially added to the evidence base of rapid tranquillisation, particularly as they have conducted high quality studies that are pragmatically conducted in the real world of rapid tranquillisation. The function of a guideline is to take that evidence and translate it into clinical practice. The NICE guideline (NICE, 2005) endeavoured to provide clinicians with recommendations to facilitate their treatment options in the circumstances of each individual event.

We suggest that for rapid tranquillisation, fast and safe medication treatment that eliminates the threat of violence with the primary aim of calming a service user to enable the use of psychosocial techniques is optimal. This should be balanced against the continued threat of violence/harm to self and others. It was the aim of the guideline development group (GDG) to promote pharmacological interventions which calmed rather than sedated the service user to enable psychosocial intervention. Haloperidol with promethazine is fast and effective at tranquillising or sedating the service user (Huf et al., 2004; 2007). However, this combination has been tested outside the UK context. The GDG considered this to be less clinically relevant to the UK context because the primary outcome of the studies had sleep as the endpoint. In the UK setting, the primary objective is to calm. Haloperidol with midazolam has been found to be effective and fast. However, midazolam is considered to have stronger respiratory effects than lorazepam (Huf et al., 2004).

Subsequent to publication of the guideline, the MHRA issued guidance which updated the SPC for haloperidol to indicate that all patients receiving this drug should have an ECG prior to initiation. It therefore cannot be assumed that haloperidol is safe in all patients. Haloperidol with lorazepam was the combination of choice in the guideline for service users experiencing psychosis. The use of haloperidol as a medication of first choice for rapid tranquillisation should now be reconsidered in the light of the need for ECG monitoring. The results of the recent olanzapine vs haloperidol with promethazine trial suggest that olanzapine can be effective with service users with moderate disturbance in line with the current recommendation in the guideline. Table 1 presents a summary of indications and contra-indications for use of the principle rapid tranquillisation medications, alongside relevant key recommendations from the NICE guideline and medication restrictions.

The outcomes measured in the TREC studies do not clearly separate tranqillising from sleep. In taking into account the guideline recommendations in Table 1, the aim of the GDG was to promote the use of pharmacological treatments to calm the patient to the extent that other psychosocial techniques could be employed to foster the ongoing treatment and care of the patient.

The guideline recommends the use of anti-muscarinic agent, such as procyclidine or benzatropine to reduce the extrapyramidal side effects of haloperidol. Huf et al. (2007) suggested that the routine use of a more sedative drug with anti-cholinergic properties (promethazine) has advantages.

The key points of this debate are:

- The service user outcomes-sleep or a state of calm
- The effective and safe elimination of the threat of violence, and the reduction of agitation and aggression

Table 1. Current key medications for rapid tranquillisation in the UK

Medication	Indicators and contra-indicators for use	NICE guideline recommendation	Current knowledge	Restrictions on use
Benzodiazepines				
Lorazepam	• Non-psychotic agitation • Calms patient • Lower respiratory effects	1.8.4.5 The service user should be able to respond to communication throughout the period of rapid tranquillisation. The aim of rapid tranquillisation is to achieve a state of calm sufficient to minimise the risk posed to the service user or to others.		Intermittent supply problems may cause difficulty in some areas of the UK
Midazolam	• More likely to sedate • Higher respiratory effects	1.8.4.17 There is not sufficient evidence that the safety of either combination of i/m haloperidol with i/m promethazine or i/m midazolam alone has been sufficiently demonstrated in the UK. However, it has been shown to be effective and relatively safe elsewhere. The GDG is therefore not able to recommend either for routine psychiatric practice in the UK.		
Anti-psychotics				
Olanzapine	• Calms rather than sedates • Effective within 1 hour	1.8.4.16 In the event of moderate disturbance in service users with psychosis, i/m olanzapine may also be considered. Intramuscular lorazepam should not be given within one hour of i/m olanzapine. Oral lorazepam should be used with caution.	Initially effective calming effect although some patients require additional medical input after one hour.	The manufacturer has issued a warning that use outside of the details contained within the Summary of Product Characteristics (SPC) may increase risk of fatality.
Haloperidol	• Effective anti-psychotic • Acute dystonic effects • Antimuscarinic required		Recent SPC for the UK since guideline requires a review of haloperidol as first medication of choice.	The SPC for haloperidol has been updated to require baseline ECG prior to treatment. Dose should be reduced if QT interval is prolonged and discontinued if the QTc exceeds 500ms.

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Combination

Haloperidol + Lorazepam	• Currently considered as first line treatment in the UK • Effective in administering low dose anti psychotic and calming patient without sedation	1.8.4.11 When the behavioural disturbance occurs in the context of psychosis, to achieve early onset of calming/sedation, or to achieve a lower dose of antipsychotic, an oral antipsychotic in combination with oral lorazepam, should be considered in the first instance.	As above re haloperidol
Haloperidol + Midazolam	• Effective and fast in sedating	1.8.4.15 Where rapid tranquillisation through oral therapy is refused, is not indicated by previous clinical response, is not proportionate response, or is ineffective, a combination of an intramuscular antipsychotic and an intramuscular benzodiazepine (i/m haloperidol and i/m lorazepam) is recommended.	
Haloperidol + Promethazine	• More likely to sedate • Less effects of dystonia • No antimuscarinic required • Service user sedated for longer periods	1.8.4.25 In very exceptional circumstances, which should be specified and recorded, i/m haloperidol in combination with i/m promethazine, or i/m midazolam alone may be considered as an alternative to intravenous administration of benzodiazepines or haloperidol. This decision should not be made by junior staff without discussion with the senior on-call psychiatrist.	

- The initial treatment of psychosis if present
- Minimal risk of drug reactions or side effects to the service user
- The continuance of other psychosocial techniques.

The gold standard for rapid tranquillisation has not been found. The TREC trials in Rio and Vellore are of a high quality. Such trials on this important area of care are difficult due to ethical issues. Most trial participants were brought to hospital without relatives and were unable to give their consent, although information on the study was provided to the participant after the acute episode (Huf et al., 2007). However, in the Raveendran et al. (2007) trial patients were entered into the study only if a relative was able to consent.

The clinician needs a hierarchy of options to be able to respond to the individual service user within the context of other support that may be provided within a particular setting.

CONCLUSIONS & CLINICAL IMPLICATIONS

Overall there is a lack of high quality clinical trial evidence surrounding the drugs used for rapid tranquillisation and their safety within UK settings. A body of evidence is developing outside the UK context. Its relevance to the UK context needs to be established. Increasing concerns about the safety of haloperidol and other antipsychotics should be taken into account when new guidelines are developed. In the meantime, clinicians need to consider prescribing from a range of options which will inevitably be influenced by the ability to safely monitor the service user's cardiac and respiratory function.

Further research is urgently needed in order to establish a gold standard medicine regime for rapid tranquilisation in the UK. The current NICE guideline is due for an update in 2009.

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GLOSSARY

Anaesthetised: A state of narcosis (unconsciousness), analgesia (lack of awareness of pain) and muscle relaxation. It is one stage beyond deep sedation. It implies loss of airway control and protective reflexes, and requires the constant attention of trained personnel to keep the patient safe. There is normally no verbal contact.

Calming: A reduction of anxiety/agitation.

Deep sedation: a reduction of consciousness and motor and sensory activity, where verbal contact is progressively lost and then (dangerously) excessive airway control and protective reflexes are lost.

Dystonia: A slow movement or extended spasm in a group of muscles.

Light sedation: A state of rest and reduction of psychological activity, but verbal contact is maintained.

Rapid tranquillisation (also called urgent sedation): The use of medication to calm/lightly sedate the service user and reduce the risk to self and/or others. The aim is to achieve an optimal reduction in agitation and aggression thereby allowing a thorough psychiatric evaluation to take place whilst allowing comprehension and response to spoken messages throughout.

Sleep: A condition of body and mind such as that which normally recurs for several hours every night, in which the nervous system is inactive, the eyes closed, the postural muscles relaxed and consciousness practically suspended.

Violence: The use of physical force which is intended to hurt or injure another person (Wright et al., 2002).

WMD: Weighted mean difference

Of all these terms 'sleep' is the one with the greatest terminological inexactitude. For the purpose of this paper we have adopted this definition from the Oxford English Dictionary. However because of its inexactitude, we have generally avoided using the term in the violence guideline.

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